REMARKS/ARGUMENTS

Claims 1-14 are rejected under 35 U.S.C. § 103 (a) as being unpatentable over U.S. Patent No. 5,961,952 ("Crane") in view of any one of JP 11099192 (JP '192), DE 29609958 ("Schott Glaswerke") or U.S. Patent No. 6,200,658 ("Walther"). The claims have not been amended. Reconsideration is respectfully requested.

On page 3, lines 2 to 5 of the Office Action dated December 29, 2007 ("Office Action"), the Examiner states:

> "Applicant is reminded that a reference does not have to go into endless detail regarding a feature, but if that reference vaguely discloses the use of such a feature, then the reference is considered for its broad teachings. Thus, Crane does not have to discuss in detail a vial to hold its composition."

Applicants agree that a reference must be considered in the context of what the document read as a whole teaches the person skilled in the art. Applicants have argued at length previously what Crane "read as a whole " teaches. It is very much with this in mind that Applicants respectfully disagree that the person skilled in the art would: (i) select a feature to improve (the vial) which the Examiner himself acknowledges is only "vaguely disclosed" over a long list of teachings of Crane; (ii) be motivated to expect the change to a coated vial to bring useful improvements; and (iii) be motivated to select one particular coating (silica) over the wide range of such coatings taught to have useful properties in the prior art. Applicants maintain that that the Examiner has still failed to justify the motivation

for steps (i)-(iii) in the absence of hindsight based on the present invention. Thus, one of the main claims in Applicant's invention comprises a radiopharmaceutical metal complex in a container having a silica coating on the inner surface.

The Examiner states on page 3 of the Office Action that:

> "While the prior art may disclose other possible vial coatings…., since the cited prior art references disclose that one possible vial coating is that with silica, the references were combined to render the instant invention obvious."

Applicants appreciate the fact that the Examiner has acknowledged that other vial coatings were known. The Examiner's logic seems to be that, because one such coating was silica, the combination is obvious. Applicants disagree with this logic, since this omits the motivation to select silica over the alternatives which the Examiner has agreed do exist. For example, silanizing containers to give clear silicone coatings have been used to prevent aqueous pharmaceuticals from adhering to the inner container walls. Furthermore, inorganic titanium/zirconium oxide coatings have been used in glass bottles to prevent pharmaceuticals and beverages from adhering to the inner walls of the bottle. Also, coatings of silicon, boron, zirconium or titanium nitrides have been used to treat the inner surface wall of a quartz, glass, or ceramic container. Containers internally coated with silicone used in the manufacture of lyophilized pharmaceutical products have been used as well. It is important to note here that Crane teaches extensively about its kits and vials being lyophilized, wherein lyophilization aids useful in the preparation of diagnostic kits are useful also for the

preparation of radiopharmaceuticals, Column 5, line 22 to Column 8, line 23. It is also known in the art that the coating inside the surface of a glass container with a silicone material substantially eliminates manufacturing problems and product deficiencies. These examples demonstrate that the person skilled in the art, without knowledge of the present invention, even if presumed to be motivated to improve Crane by the use of a coated vial, would have been faced with a wide range of possible coatings. Hence, even assuming that the person skilled in the art was motivated to improve Crane, the selection and direction of the improvement is far from clear in the absence of hindsight, and could arguably lead towards any of the aforementioned coatings instead of silica.

Furthermore, Applicants note that the law has long established that "[a] basic mandate inherent in 35 U.S.C. §103 is that "a piecemeal reconstruction of prior art patents in light of the applicants' disclosure" shall not be the basis for a holding of obviousness." *In re Kamm and Young*, 452 F.2d 1052. (C.C.P.A. 1972). Therefore, it would **not** have been obvious to one skilled in the art to modify the compositions disclosed by Crane (i.e., Tc-99m-ligand complex radiopharmaceutical diagnostic agents) to use vials having a silica-coating inner surface when there are several other various vial coatings that provide 'various advantages' for various pharmaceuticals as well. Applicant's argumentation was directed to what features the combination of references construed by the Examiner would have. In order to do that, it is perfectly proper to seek to clarify what a single reference actually discloses, since that reads on what the combination would provide. Applicant's have also argued extensively and quoted case law on whether motivation to combine references exists, in the

absence of hindsight. This too clearly addresses the combination. It is therefore factually incorrect that Applicants are only addressing references singly.

The Examiner further states on page 3, lines 6-8 of the Office Action that "the JP '192 document was cited for its teachings regarding glass containers with silica coated inner surfaces for use with radiopharmaceuticals. Hence, one should not limit its teachings to thallous chloride, but for what the document teaches as a whole." Applicants respectfully submit that this is a mischaracterization of JP '192. JP '192 refers to ^{201}Tl chloride. The chemical species is thus $Tl^{+}Cl^{-}$, which is an ionic species that would be fully ionised in aqueous solution. Ionic species are not "metal complexes". Metal complexes are in the field of coordination chemistry where an organic ligand binds to the metal *via* a covalent bond. There is therefore no correlation between the metal complexes of the present invention and the thallous chloride teaching of JP '192. Consequently, it is erroneous to refer to the chloride ion of JP '192 as a "stabiliser suitable for a metal complex". Metal complexes are an essential feature of the present claims, and Applicants respectfully request that the Examiner withdraw the previous characterization of JP '192 and confirm that JP '192 teaches only ionic species, not metal complexes. Applicants contend that the person skilled in the art would be well aware of these important differences in chemical constitution, and this in fact provides a further reason why there would be considerable doubt over whether the teaching of JP '192 could be applied successfully to radiopharmaceutical metal complexes.

The Examiner also goes on to state on page 3, line 9 of the Office Action that "Schott Glaswerke was cited for its teachings of the use of vials for pharmaceuticals".

Applicants wish to point out here that Schott Glaswerke provides no further description of a contained material such as radiopharmaceutical metal complexes, let alone a radiopharmaceutical, other than the generic reference to 'pharmaceutical'.

Applicants furthermore respectfully submit that it is well-settled law that "the mere fact that it is possible to find disclosures that might be combined in such a way to produce a new compound does not render such production obvious unless the art also contains something to suggest the desirability of the proposed combination." *In re Bergel and Stock*, 292 F.2d 955. (C.C.P.A. 1961). Applicants contend that neither Crane in view of JP '192, Schott Glaswerke, or Walther suggest the desirability to combine to make the present invention.

Applicants also submit that the present invention describes at length how radiopharmaceutical metal complexes suffer from unforeseen or variable problems that are solved using silica-coated vials. See page 4, line 17 to page 9, line 23 of the present specification. It is very important to recognise that these are not simply adsorption of radioactivity (as taught by JP '192), but also include eg. particulates and/or precipitates of unknown origin in the radiopharmaceutical liquid. Applying a prior art technology which is directed at solving solely adsorption problems would not therefore be an adequate solution for the person skilled in the art, and could not be expected to solve such diverse problems – again absent knowledge of the present invention. None of these problems, which are specific to radiopharmaceutical metal complexes, were recognized in either JP '192, Schott Glaswerke, or Walther, and hence the cited references simply cannot provide a motivation to

apply silica-coated vials to radiopharmaceutical metal complexes. The solution to the problem provided by the present claims is believed non-obvious for this reason.

The Examiner furthermore states on page 3, lines 14-17 of the Office Action that "while the prior art may disclose other possible vial coatings, the test for obviousness is not whether the prior art teaches that all vials should be coated with one particular type of coating, but what the prior art renders obvious." In response, Applicants submit that the present invention describes at length how radiopharmaceutical metal complexes suffer from unforeseen or variable problems that are solved using silica-coated vials. See page 4, line 17 to page 9, line 23 of the present specification. It is very important to recognise that these are not simply adsorption of radioactivity, but also include eg. particulates and/or precipitates of unknown origin in the radiopharmaceutical liquid. Applying a prior art technology which is directed at solving solely adsorption problems would not therefore be an adequate solution for the person skilled in the art, and could not be expected to solve such diverse problems – again absent knowledge of the present invention. None of these problems, which are specific to radiopharmaceutical metal complexes, were recognized in either JP '192, Schott Glaswerke, or Walther, and hence the cited references simply cannot provide a motivation to apply silica-coated vials to radiopharmaceutical metal complexes. The solution to the problem provided by the present claims is believed non-obvious for this reason.

Furthermore, Applicants respectfully represent that one 'could' combine references is not the standard for making a *prima facie* case of obviousness as such a

standard would only grant patentability to combinations which 'could not' be made. Indeed, if the Examiner's logic were followed, then all radiopharmaceuticals would be provided in silica-coated vials, once the cited prior art in question had published, and no one would contemplate using uncoated vials let alone any other type of coated vial that has been previously discussed. Accordingly, Applicants respectfully disagree with the Examiner's basis for finding a motivation to combine Crane with any one of JP '192, Schott Glaswerke, or Walther.

Additionally, even if JP '192, Schott Glaswerke, or Walther were to be combined with Crane in the manner suggested by the Examiner, the 'solubilization aids' taught by Crane would be rendered unnecessary, since the coated vial would (presumably) solve the adsorption problem. This contradicts the teaching of Crane, in that the absence of the 'solubilization aid' would remove an essential teaching of Crane. Neither Crane nor JP '192 teach, suggest, or disclose any additional steps to remove the solubilizer. Therefore, absent the present invention, a person skilled in art would not know that silica-coated vials would obviate the need for a solubilizer as taught by Crane. Accordingly, combining Crane with JP '192, Schott Glaswerke, or Walther in this manner is an invalid combination.

It is important for Applicants to emphasize the point that any valid combination of Crane with JP '192 would give the radiopharmaceutical metal complex plus solubilizer from Crane, in the coated vial of JP '192. As previously stated, the 'solubilization aid' or solubilizer used to solve the adsorption problem is an essential feature of Crane. The present invention, however, does not have a 'solubilization aid' or solubilizer as an essential

feature. The present invention uses silica-coated vials to solve the adsorption problem. Therefore, in order to solve the adsorption problem with using a coated vial, Crane must present an additional step of removing the solubilizer. Crane, however, does not teach, suggest, or disclose any additional steps to remove the solubilizer. Therefore, absent the present invention, a person skilled in art would not know that silica-coated vials would obviate the need for a solubilizer as taught by Crane. Accordingly, combining Crane with JP '192 in this manner is further evidence of an invalid combination.

Additionally, Applicants respectfully submit that any such combination would teach away from the present invention. 'Teaching away' simply means teaching a solution that would not lead to the claimed subject matter. As noted by the Federal Circuit:

> A reference may be said to teach away when a person of ordinary skill, upon [examining] the reference would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant. (emphasis added).
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> *Para-Ordnance Mfg. v. SGS Importers Int'l*, 73 F.3d 1085 (Fed. Cir. 1995).

Applicants respectfully submit that the mere fact that a reference may suggest an 'improvement' does not dictate that the improvement will direct one to all other 'improvements'. That is, one improvement can teach away from another, as the two improvements may diverge from each other in their teachings. The *Para-Ordnance* decision (above) clearly states that teaching away does not require a negative teaching in the prior art, the prior art need only teach other, divergent, solutions to be deemed to

teach away from an invention.

Applicants respectfully submit that it would not have been obvious to one of ordinary skill in the art to use silica-coated vials for containing the radiopharmaceuticals disclosed in Crane. As previously set forth, there are several other vial coating alternatives that could have been used in Crane.

In view of the remarks hereinabove, Applicants respectfully submit that the instant application, including claims 1-14, is in condition for allowance. Favorable action thereon is respectfully requested.

Should any other matters require attention prior to allowance of the application, it is requested that the Examiner contact the undersigned.

The Commissioner is hereby authorized to charge any fees which may be required, or credit any overpayment, to Deposit Account No. 502-665 in the name of GE Healthcare, Inc.

Respectfully submitted,

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